Original Article

Nephrotic Syndrome

Histopathological Patterns in Childhood Steroid Resistant Nephrotic Syndrome

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ABSTRACT

Objective: To determine the frequency of various histopathological lesions in children with steroid resistant nephrotic syndrome (SRNS) presenting to the Children's Hospital & the Institute of Child Health, Multan.

Study Design: Retrospective observational study

Place and Duration of Study: This study was conducted at the Department of Paediatric Nephrology, The Children's Hospital and The Institute of Child Health, Multan, Pakistan from October 2005 to December 2012.

Materials and Methods: Medical record of 152 children with SRNS, who were biopsied, was reviewed. All SRNS patients, both initial steroid resistant and late non-responders were included in the study.

Results: Out of the total 152 patients, 98 (64.5%) were males and 54 (35.5%) females, with a male to female ratio of 1.8: 1. Mean age and standard deviation of patients was μ 8.11 $\pm$ 3.58 years with age range of 1 to 15 years. Histopathological spectrum showed focal segmental glomerulosclerosis (FSGS) as the commonest (59; 38.81%) lesion followed by mesangioproliferative glomerulonephritis (MesPGN) (40; 26.31%), minimal change disease (MCD) (35; 23.02%) and mesangiocapillary glomerulonephritis (MCGN) (13; 08.55%). Four (2.63%) patients had membranous nephropathy. One patient of renal amyoidosis was also diagnosed on renal biopsy.

Conclusion: Overall FSGS was the commonest lesion followed by MesPGN, MCD, and MCGN. IgMN was an associated finding in 25% cases of MesPGN. FSGS was significantly more common among children >10 years. MCD was significantly more common among children 1-5 years. MesPGN and MCGN were significantly more common among children >5 years.

Key Words: Steroid resistant nephrotic syndrome, Renal biopsy, Histopathological pattern, Children

INTRODUCTION

Nephrotic syndrome is one of the most common renal diseases in children. It has an incidence of 2 to 7 per 100,000 population per year and a prevalence of 16 per 100,000 population.[1,2] The basic pathophysiology of all forms of nephrotic syndrome is an abnormal selective permeability barrier, leading to pathologic protein loss across the glomerular basement membrane. The hallmark of nephrotic syndrome is heavy proteinuria (>40 mg/m^2/hr), hypoalbuminemia (<2.5 g/dl), edema, and hyperlipidemia. [2,3]

It is predominantly idiopathic minimal change nephrotic syndrome (MCNS), responsible for approximately 85% of cases and characterized by its benign nature and steroid responsiveness. The majority of children will respond to steroid therapy within the first four weeks of treatment with prednisolone. Children, who do not achieve complete remission with adequate corticosteroid therapy, are considered steroid resistant (SRNS), and there is consensus about diagnostic renal biopsy in these children.[1,2,3] Observations show that about 10-20% of children with idiopathic nephrotic syndrome present with idiopathic steroid resistant nephrotic syndrome.[4,5]These children are much more likely to progress to chronic kidney disease.[6]

Various studies show an increasing trend of SRNS in children with preponderance of focal segmental glomerulosclerosis (FSGS). Azher et al in 2011, in a study in children with SRNS done in Pakistan, found that focal FSGS was the most common (28.8%) histopathological lesion, followed by IgM nephropathy (IgMN) in 17.7%, minimal change disease (MCD) and membranous nephropathy (MN) in 13.3% each, membranoproliferative glomerulonephritis (MPGN) in 11.1%, mesangial proliferative glomerulonephritis (MesPGN) in 8.8% and IgA nephropathy (IgAN) in 6.6% patients.[6] Studies done in India,[7] Nigeria[8] and Iran[9] in children with SRNS also show that FSGS was the most frequent histopathological lesion. The studies done at Sindh Institute of Urology and Transplantation (SIUT), Karachi showed an increasing prevalence of FSGS over the years in Pakistani population with higher prevalence of atypical features. This trend has immense therapeutic and prognostic significance. [10,11]

The children's Hospital and the Institute of Child Health, Multan is a tertiary care referral hospital draining a wide population area from southern Punjab, interior Sindh and Balochistan. Primary objective of this study was to find out the distribution pattern of underlying histopathological lesions in children with SRNS coming to this hospital.

MATERIALS AND METHODS

In this retrospective observational analysis, medical record of 152 children presenting with steroid resistant nephrotic syndrome, who were biopsied from October 2005 to December 2012 at the Nephrology department, the Children's Hospital and the Institute of Child Health, Multan was reviewed. All 1 to 15 years old patients from both gender, initial steroid resistant or late non-responders, were included in the study.

Patients were labeled steroid resistant if they failed to achieve complete remission (i.e three consecutive days of nil proteinuria on urinary dipstiks) after four weeks of prednisolone 60mg/m^2 plus three pulses of intravenous methylprednisolone infusions 1G / 1.73 m^2 /day on alternate days. Late non-responders were the patients who initially responded to the steroids but over a period of time became steroid resistant during a relapse.

In the prepared patients, ultrasound guided percutaneous renal biopsy was performed with Dr. J Fine Core Disposable Semiautomatic Biopsy Needle (size 16 G x 150 mm) under local anaesthesia. Two to three cores of renal tissue were taken. Biopsy specimen, preserved in formalin, were sent to the histopathologist at Dr. Zia-ud-Din University Hospital, Karachi for histopathological review by light microscopy (LM) and immunofluorescence (IF) study.

Patients name, age, date, registration number, presenting complaints, details of therapy and biopsy results were recorded by a careful review of the record and the actual biopsy reports. The outcome variable, that is histopathological lesions, was noted in the order of frequency.

Data was analyzed using statistical software SPSS-10. Descriptive statistics were applied to analyze the data. The quantitative variables were calculated by mean and standard deviation and qualitative variables by percentages and frequencies.

RESULTS

In the present study a total of 152 patients, having SRNS, who underwent ultrasound guided percutaneous RB were included. Mean (μ) age and standard deviation (±) of patients were μ 8.11, ± 3.58 years with age range of 1 to 15 years. Age at presentation was highest in the age group 6-10 years (n=62; 40.79%). There were 43 (28.28%) patients between 1-5 years and 47 (30.92%) between 11-15 years. There were 98 male (64.5%) and 54 (35.5%) female patients with a male to female ratio of 1.8:1.

Histopathological spectrum showed FSGS as the commonest (59; 38.81%) lesion the mesangio-proliferative group, followed by MesPGN (40; 26.31%), MCD (35; 23.02%) and MCGN (13; 08.55%). Amongst 10 patients (25%) had associated IgM nephropathy (IgMN), 2 patients (5%) each had IgA nephropathy (IgAN) and focal mesangial proliferation. Membranous nephropathy (MN) was detected in four patients (02.63%). One female patient of renal amyloidosis was also diagnosed on renal biopsy as shown in table I.

Table No.I: Histopathological Lesions in Patients with Steroid Resistant Nephrotic Syndrome

Lesion	No. of patients	Percentage
FSGS	59	38.81%
MesPGN	40	26.31%
MCD	35	23.02%
MCGN	13	8.55%
MN	04	2.63%
RA	01	0.66%
Total	152	100%

Key: FSGS= Focal Segmental Glomerusclerosis, MesPGN= Mesangioproliferative glomerulonephritis, MCD= Minimal Change Disease, MCGN= Mesangiocapillary Glomeulonephritis, MN= Membranous Nephropathy, RA= Renal Amyloidosis

Out of the total 43 patients between 1-5 years, 11 (25.58%) had FSGS; 21 (8.83%) had MCD and 11 (25.58%) had MesPGN. MCGN was not detected in this age group. Out of the total 62 patients between 6-10 years, 27 (43.54%) had FSGS, 10(16.12%) had MCD,19 (30.64%) had MesPGN, and 6 (09.67%) had MCGN.Four patients with MesPGN in this age group had associated IgMN and one patient had associated IgAN. Out of the 47 patients in the age group 11-15 years, 21(44.68%) had FSGS, 04 (08.51%) had MCD, 10 (21.27%) had MesPGN, 07 (14.89%) had MCGN, and 04 patients (08.51%) had IgMN. One patient had IgAN associated with MesPGN. Age wise breakup is shown in table 2.

Table No.2: Age Wise Distribution of Different Histopathological Lesions

Age (years)	No. of patients	No. of patients with FSGS	No. of patients with MesPGN	No of patients with MCD	No. of patients with MCGN	No. of patients with other lesions
1 – 5	43	11(25.58%)	11(25.58%)	21(48.83%)	Zero	Zero
6 – 10	62	27(43.54%)	19(30.64%)	10(16.12%)	06(09.67%)	Zero
11 – 15	47	21(44.68%)	10(21.27%)	04(08.51%)	07(14.89%)	05(10.64%)
Total	152	59(38.81%)	40(26.31%)	35(23.02%)	13(08.55%)	05(10.64%)

Table No.3: Sex Wise Distribution of Different Histopathological Lesions

Sex	Total No.of patients	No. of patients with FSGS	No. of patients with MesPGN	No. of patients with MCD	No. of patients with MCGN	No. of patients with other lesions
Males	98	36(36.73%)	30(30.61%)	24(24.48%)	6(6.12%)	2(2.04%)
Females	54	23(42.59%)	10(18.51%)	11(20.37%)	7(12.96%)	3(5.55%)
Total	152	59(38.81%)	40(26.31%)	35(23.02%)	13(08.55%)	5(3.29%)

FSGS was significantly more common among children > 10 years. MCD was significantly more common among children 1-5 years. MesPGN and MCGN were significantly more common among children > 5 years.

Out of the total 98 male patients, 36 (36.73%) had FSGS, 24 (24.48%) had MCD, 30 (30.61%) had MesPGN, and 6 (6.12%) had MCGN. Out of the total 54 female patients 23 (42.59%) had FSGS, 10 (18.51%) had MesPGN, 11 (20.37%) had MCD, and 7 (12.96%) had MCGN. Two males and 2 females had MN each. Sex wise breakup is shown in table 3.

DISCUSSION

Steroid resistant nephrotic syndrome is believed to be associated with a high risk of progressing to chronic kidney disease. The underlying histopathology usually affects the course of the disease as well as the response to treatment. Despite the absence of evidence based recommendations regarding the role of renal biopsy in these patients, the procedure provides important information on renal histology and outcome.[12] Present study is one of the largest series of patients over a span of 7 years from a single institution in Pakistan which describes the frequency of various histopathological lesions in children presenting with steroid resistant nephrotic syndrome at our hospital. FSGS, MesPGN, MCD and MCGN account for the majority of cases in decreasing order of frequency. IgMN is an associated finding in about a quarter of patients with MesPGN. In the landmark study by International Study of Kidney Disease in Children (ISKDC) MCD, FSGS, and MesPGN each accounted for about a quarter of children with SRNS.[13] Our study showed FSGS as the commonest lesion accounting for 38.81% of all patients followed by MesPGN which accounted for 26.31% cases. MCD was the third commonest (23.02%) lesion in our SRNS children. This is in accordance with most of the recent series reported in Pakistan and worldwide in children with SRNS.[14,15,16] Mubarak et al evaluated the spectrum of histopathological lesions in children with SRNS at a single centre in Pakistan. FSGS comprised 38.5% followed by MCD 23.2%, IgMN 13.6%, MesPGN 10.2%, MN 8.2% and MCGN 4.8%.[17] Amer et al in 2011, in a study on children with SRNS done in Peshawar, Pakistan found that FSGS was the most common histopathological lesion (28.8%), followed by IgMN in 17.7%, MCD and MN in 13.3% each, MPGN in 11.1%,MesPGN in 8.8% and IgAN in 6.6%. Safaei A and Maleknejad reported FSGS as the commonest (41%) lesion in Iranian children who underwent renal biopsy.[18] Jameela A Kari et al conducted a study in SRNS children in Kingdom of Saudi Arabia. FSGS comprised 39% of cases followed by IgMN in 28%, MesPGN in 17%, MCD and C1q nephropathy (C1qN) in 8% each and IgAN in 3%. Bonilla-Felix et al reported an increased incidence of FSGS in American children (23% before 1990 versus 47% after 1990).[19] Similarly, Srivastava et al found a higher incidence of FSGS in American children with reciprocal decline in the incidence of MCD in recent years.[20] Gulati et al found an increased incidence of FSGS in Northern and Eastern Indian populations from 20% between 1990 and 1992 to 47% between 1992 and 1996.[21] A few studies from Pakistan, Japan, France and Kuwait found a lower incidence of FSGS.[22,23,24] In our study MesPGN was the second commonest lesion after FSGS. Hafeez F et al in a study on SRNS in children in Lahore found MesPGN in 60% of cases.[25] The same histological lesion is prevalent in Chinese population.[26] A few studies found MCD as more common than FSGS in children with SRNS.[22,23,24] In our study MCD was the third most common lesion. The variable histopathologycal pattern may be related to environmental, genetic, or racial factors but the exact cause is unknown.[22] In our study IgMN was associated finding in 25 % cases with MesPGN. However, its existence as a separate entity is still controversial. Mubarak M et al published one of the largest studies of IgMN in children with idiopathic nephrotic syndrome and reported an incidence of 13.6% in children with SRNS.[27]

While evaluating clinicopathological spectrum of renal biopsies in children, our study showed a male predminance (M:F = 1.7) which is consistent with many series from around the world.[3,4,5] Age-wise break up showed a higher incidence of MCD in younger children less than 5 years age and a higher incidence of FSGS in older children more than 10 years age. MesPGN and MCGN were significantly more common in children older than 5 years. This disparity may be explained by the fact that some patients with MCD on a first biopsy may have FSGS if a biopsy is done later in the disease, especially if they are persistently steroid resistant or if they have developed secondary steroid resistance. Since it is only necessary to identify a single area of focal hyalinosis in a single glomerulus to diagnose FSGS, the question of whether FSGS was present all along but missed on the first biopsy because a representative lesion was not included in the biopsy, or whether "true"

MCD can evolve into FSGS, is unanswerable. There are grounds for believing that the lesions of FSGS arise as a consequence of unremitting heavy proteinuria, rather than being the cause of it. If this is true, it follows that steroid resistant cases are more likely to develop FSGS than steroid responsive cases, in whom proteinuria is intermittent.[28] Though, our study was a retrospective, observational analysis, it gives a good view of the underlying histopathological lesions prevailing in our SRNS patients. But prospectively designed, multicenter studies involving larger sample size would be the better representative. This would guide us to plan better management strategies for these patients.

CONCLUSION

The histopathological pattern in our children with SRNS shows FSGS as the commonest lesion followed by MesPGN and MCD. IgMN was associated with a quarter of patients with MesPGN.

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